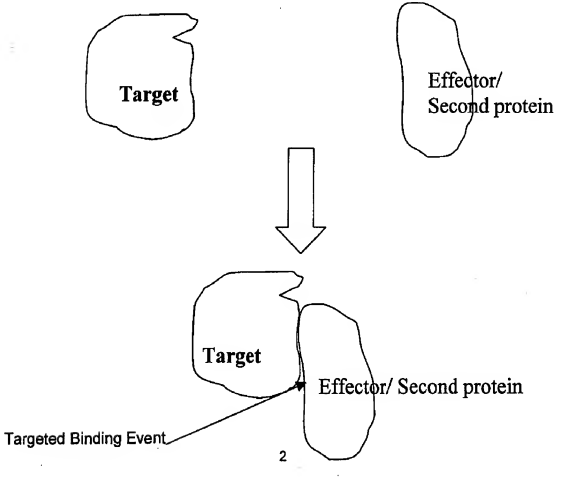
REMARKS

In the Final Rejection of June 17, 2003, the Examiner maintained a number of rejections raised in the previous office action.

REVIEW OF INVENTION

The invention is directed to methods of inhibiting a protein-protein interaction in a host, e.g., for therapeutic purposes. For example, the invention is directed to methods of inhibiting an in vivo biochemical event caused by two proteins, e.g., a target protein and an effector protein (referred to as a second binding protein in the claims), by inhibiting the binding of the second protein to the target protein. The targeted binding event between a target protein and an effector/second binding protein that is the subject of the claims is illustrated below:



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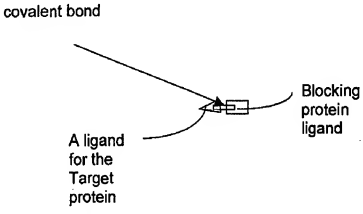
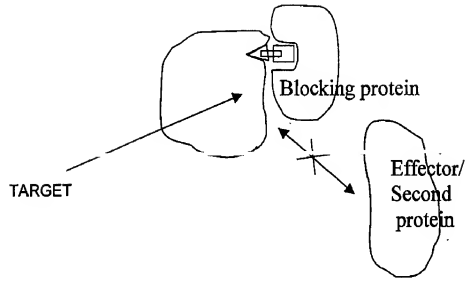
Traditionally, such methods have been accomplished using inhibitor molecules. However, the size of the inhibitor molecule needed to provide for the blocking activity can be limiting with respect to practical use in therapeutic applications. As such, there has been an ongoing need in the field to identify small molecule inhibitors.

The present invention is based on the ingenious manner in which the inventors have satisfied this need for a small molecule effective inhibitor. The invention employs a bifunctional molecule that recruits a blocking protein in vivo to produce an inhibiting complex. The bifunctional molecule is made up of a target protein ligand and a second ligand that binds to a blocking protein. A representation of the bifunctional molecules employed in the invention is provided below:



When administered to the host, the bifunctional molecule bonds non-covalently to the target protein and a blocking protein, thereby inhibiting binding of the effector or second binding protein to the target. This process of simultaneously and non-covalently binding to the target protein and the blocking protein and thereby inhibiting binding of the effector/second binding protein to the target is illustrated below:



As the bifunctional molecule is a small molecule, i.e., less than 5000 daltons, that nonetheless turns into an effective inhibitor complex when it binds to the blocking protein, it satisfies the above felt-need in the field of pharmaceutical inhibitor active agents.

MAINTAINED REJECTIONS

The Examiner has maintained the rejection of Claims 16-24 under 35 U.S.C. § 112, 2nd ¶ for specific reasons A and B. Each of these reasons is addressed separately below.

With respect to reason A, the Examiner contends that the term "an effective amount" in the Claim 16 is indefinite because " the claim fails to state the function which is to be achieved." citing In re Frederiksen and Nielsen, 102 USPQ 35.

However, the situation is not analogous to *In re Frederiksen and Nielsen*. The claim in question in *In re Frederiksen and Nielsen* read:

6. An improvement in the production of penicillin by submerged culture which comprises providing a culture medium containing nutrient material and associating with said culture medium a Penicillium mold of the notatum chrysogenum group and an effective amount of the diethylamino ethanol ester of phenaceturic acid.

As can be seen in the above claim 6, there is no functional phrase that can be linked with the phrase "an effective amount."

In contrast to the above claim 6 that was under consideration in *In re Frederiksen and Nielsen*, the function of the effective amount is recited in claim 16 of the present application. Specifically, Claim 16 of the present application states that the amount administered is effective:

"to simultaneously bind said first target protein and said blocking protein to produce a tripartite complex that inhibits said binding event of said second binding protein to said first target protein."

Furthermore, the ordinary practitioner would understand that the effective amount is a matter of routine, and can be determined in each case to provide the inhibiting function, without undue experimentation.

Accordingly, the rejection of Claim 16 for issue A may be withdrawn.

With respect to Issue B, the Examiner asserts that the claim is indefinite because "the method does not clearly outline how the second protein and the blocking protein interact such that inhibition of the first and second is accomplished."

The Examiner, in making this rejection, appears to believe that the law requires a method step to state in th claim how the method is working. However, such is not required by the law. Otherwise, numerous issued and valid pharmaceutical method claims would be deemed improper for indefiniteness, because they simply read: "A method of treating disease X by administering an effective amount of compound Y." Such claims are routinely granted and not indefinite, even though they do not recite the mechanism of how Y is treating X.

Furthermore, an inventor is not required to know how or why his invention works (See in re Spada, 15 U.S.P.Q.2D 1655 (Fed.Cir. 1990) nor is it required to set forth a theory of operation in the specification or claims. Donner, Patent Prosecution, (BNA, 1999) p 37. It is sufficient to teach a person of ordinary skill in the art how to make and use the invention, and to distinctly point out the subject matter of the invention. Thus, Sec. 112 requires the inventor to say what steps are performed and how to perform them; not *why* they should be performed, nor *why* any given action has the effect desired.

In view of the above, it is respectfully submitted that Claim 16 fully complies with the requirements of 35 U.S.C. §112, 2nd ¶, and that the rejection of Claim 16 for issue B may be withdrawn.

In sum, in view of the above remarkes, the Examiner is respectfully requested to withdraw the rejection of Claims 16-24 under 35 U.S.C. § 112, 2nd ¶.

The Examiner has also maintained the rejection of 35 U.S.C. § 112, 2nd ¶ for the asserted reason that essential steps are omitted because the claim does not include the following: "(I) A sample and reagent contacting step; (II) the binding or complex formation of a labeled product, the detection of the labeled product, and (III) a correlation step.

However, the claim preamble of Claim 16 reads:

> A method of inhibiting a binding event between a first target protein and a second binding protein in a host

As such, what is being claimed is simply a method of inhibiting a binding event in a host.

Accordingly, the only required method step for such a claim is the administration of agent to the host that inhibits the binding event. Such a step is clearly present in the body of the claim.

The claim does not require that one prove the binding event was inhibited, or detect the inhibition of the binding event, as such a requirement is not recited in the preamble.

The invention as claimed in Claim 16 is concerned with administering a small molecule to inhibit a binding event *in vivo* in a host. The claims are not directed to an assay or screen for discovering such molecules, nor are such assay steps required in the claim. Should such testing be desired, it can be done according to assay methods well known in the art, as explained in the specification, but such tests are *not* necessary to the claimed method and would be a different invention from the one that the applicants are prosecuting in this application.

As such, it is respectfully submitted that Claims 16-24 do not omit essential steps and that this rejection under 35 U.S.C. § 112, 2nd ¶ can be withdrawn.

Claims 16-24 r main rejected under 35 U.S.C. § 102(b) over Griffith. The Examiner's maintainence of this rejection appears to be based on th Examiner's equating of the FKBP12/FK506 complexes disclosed in Griffith with the bifunctional molecules employed in the claimed methods.

However, the FKBP12/FK506 complexes disclosed in Griffith are not the same as the bifunctional molecules employed in the claimed methods.

The bifunctional molecule employed in the claimed methods is

> a non-naturally occurring bifunctional inhibitor **molecule** of **less than 5000 daltons** consisting of:
> (a) a target protein ligand that specifically binds to said first target protein; and
> (b) a blocking protein ligand that specifically binds to a blocking protein,

The Griffith complex was produced by combining the purified recombinantly produced FKBP12 with the FK506 and allowing the two molecules to non-covalently bind to each other to produce the complex. As such, the FK506-FKBP12 complexes are not single molecules, but instead two different molecules noncovalently and specifically bound to each other. As such, the FK506-FKBP12 complexes are clearly excluded from the claim scope which refers to the bifunctional agent as **a single molecule**.

Furthermore, it is again pointed out that the FK506-FKBP12 complexes are complexes that include FKBP12, which is a protein that is an approximately 12kD protein. As such, the complexes are clearly outside the weight limitation of the bifunctional molecules of the claim. 12,000 Daltons.

As such, the FK506-FKBP12 complexes are not bifunctional molecules as defined in the claimed methods (which require covalent bonding of the two

ligands to each other), because the distinct components are not covalently bonded to one another and exceed the 5000 dalton weight limitation.

Accordingly, Griffth does not anticipate Claims 16 to 24 and this rejection may be withdrawn.

The rejection of Claims 16-21 and 24 under 35 U.S.C. §102 (b) as being anticipated by Varshavsky et al was also maintained.

This rejection is based on the equation by the Examiner of the reference's a-b-l trifunctional molecule to the claimed bifunctional molecules. In the a-b-i molecules of the cited reference, the molecules include three distinct ligands: (i) for enzyme I, (a) for protein A and (b) for protein B.

Such trifunctional molecules are clearly excluded from the claimed methods, which recite:

> a **non-naturally occurring bifunctional inhibitor molecule** of less than 5000 daltons **consisting of:**
> (a) a target protein ligand that specifically binds to said first target protein; and
> (b) a blocking protein ligand that specifically binds to a blocking protein,

As such, trifunctional molecules are excluded from the claims.

Furthermore, the claims require that the bifunctional molecule employed in the subject methods be one that can

"simultaneously bind said first target protein and said blocking protein to produce a tripartite complex ..."

Nowhere in the Varshavsky reference is the idea taught or suggested to make a tripartite complex of:

1) a target protein;

2) a bifunctional molecule; and

3) blocking protein.

Instead, all that is taught or suggested by Varshavsky is the production of binary complexes of either a **trifunctional** molecule (a-b-i) and its target or a trifunctional molecule and a second protein that prevents the trifunctional molecule from binding to the target.

Specifically, as can be seen in Figure 2, when a-b-i binds to I, only a binary complex made up of a-b-i and I is produced. No tripartite complexes are produced in any of the schemes disclosed in Figure 2, because there are no complexes shown that are made up of three distinct moieties non-covalently but specifically bound to each other.

It is respectfully submitted that the Examiner is incorrectly reading the teachings of Varshavsky. Only binary complexes are produced in any of the schemes and figures shown or discussed in Varshavsky. None of the schemes discussed or shown in Varshavsky teach the production of a tripartite complex produced by the non-covalent specific binding of a target protein, a bifunctional molecule and a blocking protein, much less one that prevents the binding of a target protein to a second binding/effector protein.

In sum, nowhere in the Varshavsky reference is the idea taught or suggested to make a tripartite complex of a target protein, a bifunctional molecule and blocking protein. Instead, all that is taught or suggested is binary complexes of either a trifunctional molecule and its target or a trifunctional molecule and a second protein that prevents the trifunctional molecule from binding to the target.

Since Varshavsky only t aches or suggests methods in which a trifunctional molecule is employed, Varshavsky fails to anticipat the claims under 35 U.S.C. §102 (b) and this rejection may be withdrawn.

Finally, Claims 22 and 23 remain rejected under 35 U.S.C. § 103(a) over Varshavsky in view of Pouletty, for the asserted reason that Varshavsky taught all of the elements of the claimed method but for the extracellular production of tripartite complexes, which element is assertedly made up by Pouletty.

However, Varshavsky only teaches or suggests the use of a trifunctional compound, a-b-i, and therefore in no way teaches or suggests the use of a bifunctional compound, as is required by the claimed methods.

Furthermore, as pointed out above, Varshavsky is fundamentally deficient in failing to teach or even suggest the production of tripartite complexes. In fact, Varshavsky actually teaches away from the production of tripartite complexes for the following reasons. Varshavsky's whole paper is directed to ways of making drugs more selective. The approach suggested is to link the drug to a second ligand that will bind to a protein in a cell where one does not want drug activity, such that when the trifunctional (a-b-i) molecule binds to the second protein in the cell where drug activity is not wanted, the trifunctional molecule cannot bind to the drug target. As such, drug activity is limited to those cells that lack the second protein. For this scheme to work, binding to the second protein, i.e., the blocking protein, must prevent the trifunctional molecule (a-b-i) from binding to the target. If the trifunctional molecule binds to the target, one would still get drug activity and selectivity would not be achieved. **As such, Varshavsky's scheme only works if the trifunctional molecule cannot form a tripartite complex with a target protein and blocking protein at the same time, i.e., cannot simultaneously bind to a target protein and a blocking protein.**

This requirement of Varshavsky is directly opposite to the claimed methods, where one must produce a tripartite complex between a target protein, a bifunctional molecule and a blocking protein.

As such, Varshavsky teaches away from the claimed methods because Varshavsky teaches methods in which tripartite complexes must not be produced, but instead only binary complexes are produced. **Because Varshavsky teaches away from methods in which tripartite complexes are produced, this reference fails to suggest the production of tripartite complexes, a required element of the claimed methods.**

As Pouletty was been cited solely for the extracellular production site, the Pouletty teaching is incapable of making up the above fundamental deficiency in Varshavsky.

In sum, because the combined teaching of Varshavsky and Pouletty fails to teach or suggest methods of using bifunctional molecule as claimed in Claims 22 and 23, the rejection of Claims 22 and 23 under 35 U.S.C. § 103(a) over Varshavsky in view of Pouletty may be withdrawn.

CONCLUSION

In view of the above amendments and remarks, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issuance.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815.

Respectfully submitted,

Date: October 17, 2003

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